3

A Model for the Development of Tolerable Upper Intake Levels

BACKGROUND INFORMATION

The framework for developing Dietary Reference Intakes (DRIs) includes an evaluation of the Tolerable Upper Intake Level (UL) for nutrients. The UL in this context refers to an intake ordinarily in excess of the Recommended Dietary Allowance (RDA) or Adequate Intake (AI) and associated with negligible risk of adverse health effects; it does not include consideration of the level of intake with minimal risk of dietary deficiency. A model has been developed that is generally applicable to the problem of identifying upper levels of nutrient intake.

Like all chemical agents, nutrients can produce adverse health effects if intakes from any combination of food, water, nutrient supplements, and pharmacologic agents are excessive. It is also the case that some levels of nutrient intake above those associated with any documented benefit pose no likelihood or risk of adverse health effects in normal individuals. In actuality, it is not possible to identify a single "risk-free" intake level for a nutrient that can be applied with certainty to all members of a population. However, it is possible to develop intake levels that are unlikely to pose risks of adverse health effects to most members of the healthy population, including sensitive individuals, throughout the life stage, excepting in some cases discrete subpopulations (for example, those with genetic predispositions or certain disease states) that may be especially vulnerable to one or more adverse effects.

The term *Tolerable Upper Intake Level* is defined as the maximum

level of total chronic daily intake of a nutrient judged to be likely to pose no risk of adverse health effects to the most sensitive members of the healthy population. It is developed by applying the model described. The term *tolerable* is chosen because it connotes a level of intake that can, with high probability, be tolerated biologically by individuals, but it does not imply acceptability of that level in any other sense. Particularly, it should not be inferred that nutrient intakes greater than the RDA are recommended as being beneficial to an individual. The term *adverse effect* is defined as any significant alteration in the structure or function of the human organism (Klaassen et al., 1986) or any impairment of a physiologically important function, in accordance with the definition set by the joint World Health Organization, Food and Agriculture Organization of the United Nations, and International Atomic Energy Agency (WHO/FAO/IAEA) Expert Consultation in *Trace Elements in Human Nutrition and Health* (WHO, 1996).

A MODEL FOR DERIVATION OF TOLERABLE UPPER INTAKE LEVELS

The possibility that the methodology used to derive ULs might be reduced to a mathematical model that could be generically applied to all nutrients was considered. Such a model might have several potential advantages, including ease of application and assurance of consistent treatment of all nutrients. It was concluded, however, that the current state of scientific understanding of toxic phenomena in general, and nutrient toxicity in particular, is insufficient to support the development of such a model. (A fuller discussion of this problem is set forth in the section on "Risk Assessment and Food Safety".) Scientific information regarding various adverse effects and their relationships to intake levels varies greatly among nutrients, depending on the nature, comprehensiveness, and quality of available data and the uncertainties associated with the unavoidable problem of extrapolating from the circumstances under which data are developed (for example, in the laboratory or clinic) to other circumstances (for example, to the healthy population). Given the current state of knowledge, any attempt to capture in a mathematical model all the information and scientific judgments that must be made to reach conclusions regarding ULs would not be consistent with contemporary risk assessment practices.

An appropriate model for the derivation of ULs consists, then, not of a mathematical formula, but rather a set of scientific factors that always should be considered explicitly. The framework under

which these factors are organized is called *risk assessment.* Risk assessment as first set forth by the National Research Council (NRC) in its 1983 report, and as affirmed by another NRC committee in 1994 (NRC, 1994), is a systematic means of evaluating the probability of occurrence of adverse health effects in humans from excess exposure to an environmental agent (in this case, a nutrient) (FAO/WHO, 1995; Health Canada, 1993). The hallmark of risk assessment is the requirement to be explicit in all of the evaluations and judgments that must be made to document conclusions.

RISK ASSESSMENT AND FOOD SAFETY

Basic Concepts

Risk assessment is a scientific undertaking having as its objective a characterization of the nature and likelihood of harm resulting from human exposure to agents in the environment. The characterization of risk typically contains both qualitative and quantitative information and includes a discussion of the significant scientific uncertainties in that information. In the present context, the agents of interest are nutrients, and the environmental media are food, water, and nonfood sources such as nutrient supplements and over-the-counter pharmaceutical preparations. Additional human exposure to some dietary agents, including nutrients, sometimes occurs through other media, such as air. For example, inhaling zinc oxide in an industrial setting is associated with metal fume fever (Hodgson et al., 1988). The applications of risk assessment to nutrients and other food components in general are the subject of this section, although the principles and methods discussed are more broadly applicable.

Performing a risk assessment results in a characterization, with due attention to scientific uncertainties, of the relationships between exposure(s) to an agent and the likelihood that adverse health effects will occur in members of exposed populations. Scientific uncertainties are an inherent part of the risk assessment process and are discussed below. Deciding whether the magnitude of exposure is "acceptable" or "tolerable" in specific circumstances is not a component of risk assessment; this activity falls within the domain of what is called *risk management.* Risk management decisions depend on the results of risk assessments but may involve additional considerations, such as the public health significance of the risk, the technical feasibility of achieving various degrees of risk control, and the economic and social costs of this control. Because

there is no single, scientifically definable distinction between "safe" and "unsafe" exposures, risk management necessarily incorporates components of sound, practical decision making that are not addressed by the risk assessment process (NRC, 1983, 1994).

Although a risk assessment requires that information be organized in rather specific ways, its conduct does not require any specific scientific methodologies for evaluating that information. Rather, it asks risk assessors to evaluate scientific information using what are, in their judgments, appropriate methodologies and to make explicit the bases for their judgments. Risk assessment also requires explicit recognition of uncertainties in risk estimates and the acknowledgment, when appropriate, that alternative interpretations of the available data may be scientifically plausible (NRC, 1994; OTA, 1993).

Risk assessment is subject to two types of scientific uncertainties: (1) those related to data and (2) those associated with any inferences that are required when directly applicable data are not available (NRC, 1994). Data uncertainties arise in the evaluation of information obtained from the epidemiology and toxicology studies and investigations of nutrient intake levels that are the basis for risk assessments. The use of data from experimental animals to estimate responses in humans, and the selection of so-called uncertainty factors to estimate inter- and intraspecies variabilities in response to toxic substances are examples of the use of inferences in risk assessment. Uncertainties regarding the appropriate inferences to be made arise whenever attempts are made to estimate or predict adverse health effects in humans (in which there are often inadequate or nonexistent direct empirical data) based on extrapolations of data obtained under dissimilar conditions (for example, experimental animal studies). Data on nutrient toxicity are generally available from studies in human populations and, therefore, may not be subject to the same uncertainties (related to interspecies extrapolations) associated with the available data on nonessential chemicals. Options for dealing with uncertainties are discussed below and in detail in Appendix C.

Steps in the Risk Assessment Process

Although various terms are used to describe the specific organizing steps of the risk assessment process (for example, FAO/WHO, 1995), there appears to be widespread agreement among risk assessors on the content of those steps. The organization of risk assessment in this report is based on a model proposed by the NRC (1983,

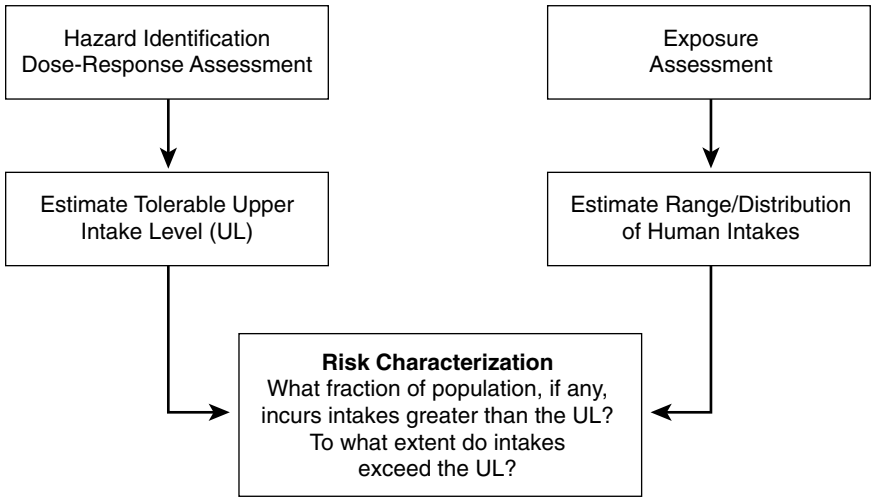

FIGURE 3-1 Risk assessment model for nutrient toxicity.

1994). The steps of risk assessment as applied to nutrients are as follows (see also Figure 3-1):

- Step 1. *Hazard identification* involves the collection, organization, and evaluation of all information pertaining to the toxic properties of a given nutrient. It concludes with a summary of the evidence concerning the capacity of the nutrient to cause one or more types of toxicity in humans.
- Step 2. *Dose-response assessment* determines the relationship between nutrient intake (dose) and adverse effect (in terms of incidence and severity). This step concludes with an estimate of the UL—the maximum level of total chronic daily nutrient intake judged unlikely to adversely affect the most sensitive individuals in a healthy population. ULs may be developed for various age groups within the population.
- Step 3. *Exposure assessment* evaluates the distribution of usual total daily nutrient intakes among members of a healthy population.
- Step 4. *Risk characterization* summarizes the conclusions from Steps 1 through 3 and evaluates the risk. Generally, the risk is expressed as the fraction of the exposed population, if any, having nutrient intakes (Step 3) in excess of the estimated UL (Steps 1 and 2). The characterization also discusses, where possible, the magnitude of any such excesses. Scientific uncertainties associated with

both the UL and the intake estimates are described so that risk managers understand the degree of scientific confidence they can place in the risk assessment.

The risk assessment contains no discussion of recommendations for reducing risk; these are the focus of risk management.

Thresholds

A principal feature of the risk assessment process for noncarcinogens is the long-standing acceptance that no risk of adverse effects is expected unless a threshold dose (or intake) is exceeded. The adverse effects that may be caused by a nutrient almost certainly occur only when the threshold dose is exceeded. The critical issues concern the methods used to identify the approximate threshold of toxicity for a large and diverse human population. Because most nutrients are not considered to be carcinogenic in humans, the approach to carcinogenic risk assessment (EPA, 1996) will not be discussed here.

Thresholds vary among members of a healthy population (NRC, 1994). If, for any given adverse effect, the distribution of thresholds in the population could be quantitatively identified, then it would be possible to establish ULs by defining some point in the lower tail of the distribution of thresholds that would be protective for some specified fraction of the population. However, the current state of biomedical sciences is insufficiently developed to allow identification of the distribution of thresholds in all but a few, well-studied cases (for example, acute toxic effects or for chemicals such as lead, where the human database is very large). The method for identifying thresholds for a healthy population described here is designed to ensure that almost all members of the population will be protected, but it is not based on an analysis of the theoretical (but practically unattainable) distribution of thresholds. There is considerable confidence, however, that the threshold derived by application of the model, which becomes the UL for nutrients, lies very near the low end of the theoretical distribution, and is the end representing the most sensitive members of the population. Note that for some nutrients, there may be distinct subpopulations that are not included in the general distribution because of their unusual genetic predispositions to toxicity. Such distinct groups may not be protected by the UL.

The Joint FAO/WHO Expert Commission on Food Additives and various national regulatory bodies have identified certain factors

that account for interspecies and intraspecies differences in response to the hazardous effects of substances and to account for other uncertainties (WHO, 1987). These factors are used to make inferences about the threshold dose of substances for members of a large and diverse human population from data on adverse effects obtained in epidemiological or experimental studies. These factors are applied consistently when data of specific types and quality are available. They are typically used to derive acceptable daily intakes for food additives and other substances for which data on adverse effects are considered sufficient to meet minimum standards of quality and completeness (FAO/WHO, 1982). These adopted or recognized factors have sometimes been coupled with other factors to compensate for deficiencies in the available data and other uncertainties regarding data.

The UL is generally based on a no-observed-adverse-effect level (NOAEL) that is identified for a specific circumstance in the hazard identification and dose-response assessment steps of the risk assessment. The NOAEL is the highest intake (or experimental dose) of a nutrient at which no adverse effects have been observed in the individuals studied. If there are no adequate data demonstrating a NOAEL, then a lowest-observed-adverse-effect level (LOAEL) may be used. A LOAEL is the lowest intake (or experimental dose) at which an adverse effect has been identified. The derivation of a UL from a NOAEL (or LOAEL) involves a series of choices about what factors should be used to deal with uncertainties. Uncertainty factors (UFs) are attempts both to deal with gaps in data (for example, lack of data on humans or lack of adequate data demonstrating a NOAEL) and with incomplete knowledge regarding the inferences required (for example, the expected variability in response within the human population). The problems of both data and inference uncertainties arise in all steps of the risk assessment. A discussion of options available for dealing with these uncertainties is presented below and in greater detail in Appendix C.

A UL is not, in itself, a description of human risk. It is derived by application of the hazard identification and dose-response evaluation steps (Steps 1 and 2) of the risk assessment model. To determine whether exposed populations are at risk requires an exposure assessment (Step 3, evaluation of their intakes of the nutrient) and a determination of the fractions of those populations, if any, whose intakes exceed the UL (for example, those whose intakes exceed the estimated threshold for toxicity). In the exposure assessment and risk characterization steps (Steps 3 and 4; described in the respective chapters for each nutrient), the ninety-fifth percentile in-

take level for exposed populations will be used as a basis in determining whether these populations are at risk. The remaining sections of this chapter deal with the derivation of ULs for nutrients (Steps 1 and 2).

APPLICATION OF THE RISK ASSESSMENT MODEL TO NUTRIENTS

This section provides guidance for applying the risk assessment framework (the "model") discussed above to the derivation of ULs for nutrients.

Special Problems Associated with Substances Required for Human Nutrition

Although the risk assessment model outlined above can be applied to nutrients to derive ULs, it must be recognized that nutrients possess some properties that distinguish them from the types of agents for which the risk assessment model was originally developed (NRC, 1983).

In the application of accepted standards for assessing risks of environmental chemicals to the risk assessment of nutrients, a fundamental difference between the two categories must be recognized: nutrients are essential for human well-being and often for life itself within a certain range of intakes, although they may share with other chemicals the production of adverse effects at excessive exposures. History has shown that the consumption of balanced diets is consistent with the development and survival of humankind over many millennia. This observation limits the need for some of the large uncertainty factors that have been found appropriate for risk assessment of nonessential chemicals. Moreover, data on nutrient toxicity are often available from studies in human populations and are therefore not usually subject to the degree of uncertainty associated with the types of data available on nonessential chemicals.

In addition, there is no evidence to suggest that nutrients consumed at the RDA or AI and as part of unfortified diets present a risk of adverse effects to the healthy population. Possible exceptions to this generalization relate to specific geochemical areas with excessive environmental exposures to certain trace elements (for example, selenium) and to rare case reports of adverse effects associated with highly eccentric consumption of specific foods. Data from such findings are not useful for setting ULs for the general U.S. population. It is clear, however, that the addition of high

doses of nutrients to a diet, either through fortification or through nonfood sources such as nutrient supplements and over-the-counter pharmaceutical preparations, may at some level pose the risk of adverse health effects. The data available on such effects of specific nutrients pertain in some cases only to intakes from fortificants or nonfood sources; in other cases, they pertain to total intakes from all sources. Therefore, the derived ULs for some nutrients refer to total intakes and for others only to intakes from fortified foods or nonfood sources. Discussion of the UL for each nutrient clarifies which use of the term applies.

Differences in the effects of nutrients from fortified foods or nonfood sources and those that are endogenous constituents of foods may be due to factors such as the chemical form of the nutrient, the timing of the intake and amount consumed in a single bolus dose, the matrix supplied by the food, and the relation of the nutrient to the other constituents of the diet. Nutrient requirements and food intake are related to the metabolizing body mass, which is also a measure, although at times indirect, of the space in which the nutrients are distributed. This relation between food intake and space of distribution supports homeostasis, which maintains nutrient concentrations in that space within a range compatible with health. This is generally the case for individuals whose food intake corresponds to their energy needs and lean body mass. However, excessive intake of a single nutrient from nonfood sources can compromise this homeostatic mechanism. Such elevations alone may pose risks of adverse effects; imbalances among the concentrations of mineral elements (for example, calcium, iron, zinc, copper) can result in additional risks (Mertz et al., 1994). These reasons and those discussed previously support the need to include the form and pattern of consumption as an important component of the assessment of micronutrients.

Consideration of Variability in Sensitivity

The risk assessment model outlined in this chapter is consistent with classical risk assessment approaches in that it must consider variability in the sensitivity of individuals to adverse effects. A discussion of how variability is dealt with in the context of nutritional risk assessment is provided here.

Physiological changes and common conditions associated with growth and maturation that occur during an individual's lifespan may influence sensitivity to nutrient toxicity. For example, (1) sensitivity increases with declines in lean body mass and with declines

in renal and liver function that occur with aging; (2) sensitivity changes in direct relation to intestinal absorption or intestinal synthesis of nutrients (for example, vitamin K, biotin); (3) in the unborn fetus and newborn infant, sensitivity increases due to active placental transfer, accumulation of certain nutrients in the amniotic fluid, rapid development of the brain, and with secretion of nutrients in human milk; and finally, (4) sensitivity increases with decreases in the rate of metabolism of nutrients. Therefore, to the extent possible, ULs are developed for each separate age or life stage group. Examples of life stage groups that may differ in terms of nutritional needs and toxicological sensitivity include infants and children, the elderly population, and women during pregnancy or lactation.

Even within relatively homogeneous life stage groups, there is a range of sensitivities to toxic effects. The model described below is directed at the derivation of ULs for members of the healthy population, divided into various life stage groups. It accounts for normally expected variability in sensitivity, but it excludes subpopulations with extreme and distinct vulnerabilities due to genetic predisposition or other considerations. Including data on subpopulations that have unusually high and distinct sensitivities to adverse effects would result in ULs that are significantly lower than are needed to protect most people. Subpopulations needing special protection are better served through the use of public health screening, health care providers, product labeling, or other individualized strategies. Such subpopulations may not be at "negligible risk" when their intakes reach the UL developed for the healthy population. The extent to which a subpopulation becomes significant enough to be assumed to be representative of a healthy population is an area of judgment and is discussed in the chapters for each nutrient.

Bioavailability

Bioavailability of a dietary nutrient can be defined as its accessibility to normal metabolic and physiological processes. Bioavailability determines a nutrient's beneficial effects at physiological levels of intake and affects the nature and severity of toxicity due to excessive intakes. Modulating components include: other dietary components; concentration and chemical form of the nutrient in food, water, nutrient supplements, and over-the-counter pharmaceutical preparations; the nutritional, physiological, and disease state of the individual; and excretory losses. Because of the considerable variability in nutrient bioavailability in humans, bioavailability data for specific nutrients must

be considered and incorporated by the risk assessment process. Situations related to nutrient bioavailability, described in the following two sections, are relevant to establishing ULs.

Nutrient Interactions

It is well established that certain nutrients interact with each other to alter bioavailability. For example, dietary interactions can affect the chemical forms of elements at the site of absorption through ligand binding or changes in the valence state of an element (Mertz et al., 1994). Phytates, phosphates, and tannins are among the most powerful depressants of bioavailability, and organic acids, such as citric and ascorbic acid, are strong enhancers for some minerals and trace elements. Thus, dietary interactions strongly influence the bioavailability of elements by affecting their partition between the absorbed and the nonabsorbed portion of the diet. The large differences of bioavailability ensuing from these interactions support the need to specify the chemical form of the nutrient when setting ULs. Dietary interactions can also alter nutrient bioavailability through their effect on excretion. For example, dietary intake of protein, phosphorus, sodium, and chloride all affect urinary calcium excretion and hence calcium bioavailability (see Chapter 4). Interactions that significantly elevate or reduce bioavailability may represent adverse health effects.

Although it is critical to include knowledge of any such interactions in the risk assessment, it is difficult to evaluate the possibility of interactions without reference to a particular level of intake. This difficulty can be overcome if a UL for a nutrient or food component is first derived based on other measures of toxicity. Then an evaluation can be made of whether intake at the UL has the potential to affect the bioavailability of other nutrients.

Other Relevant Factors Affecting Bioavailability of Nutrients

In addition to nutrient interactions, other considerations have the potential to influence nutrient bioavailability, such as the nutritional status of an individual and the form of intake. These issues should be considered in the risk assessment. The absorption and utilization of most minerals, trace elements, and some vitamins are a function of the individual's nutritional status, particularly regarding the intake of other specific nutrients such as iron (Barger-Lux et al., 1995; Mertz et al., 1994).

With regard to the form of intake, minerals and trace elements

often are less readily absorbed when they are part of a meal than when taken separately or when present in drinking water (NRC, 1989b). The opposite is true for fat-soluble vitamins whose absorption depends on fat in the diet. ULs must therefore be based on nutrients as part of the total diet, including the contribution from water. Nutrient supplements that are taken separately from food require special consideration, since they are likely to have different availabilities and therefore may present a greater risk of producing toxic effects.

STEPS IN THE DEVELOPMENT OF THE UL

Hazard Identification

The collection of scientific data for developing ULs is discussed in Chapter 2. Based on a thorough review of the scientific literature, the hazard identification step outlines the adverse health effects that have been demonstrated to be caused by the nutrient. As noted in the section above on nutrient interactions, interference with nutrient bioavailability is not considered an adverse effect at this stage; rather it is considered only after more conventional adverse responses are evaluated and a tentative UL is derived.

The primary types of data used as background for identifying nutrient hazards in humans are as follows:

- *Human studies.* Although data from controlled studies in humans are the basis for establishing nutritional requirements, the number of controlled human toxicity studies conducted in a clinical setting are, for ethical reasons, very limited and are useful for identifying only very mild and completely reversible adverse effects. Nevertheless, the available human data provide the most relevant kind of information for hazard identification and, when they are of sufficient quality and extent, are given greatest weight. Observational studies that focus on well-defined populations with clear exposures to diverse specific nutrient intake levels are useful for establishing a relationship between exposure and effect. Observational data in the form of case reports or anecdotal evidence are used for developing hypotheses that can lead to knowledge of causal associations.
- *Animal studies.* The majority of the available data used in regulatory risk assessments comes from controlled laboratory experiments in animals, usually mammalian species other than humans (for example, rodents). Such data are used in part because human data on nonessential chemicals are generally less available than human data on es-

sential substances. Because well-conducted animal studies can be controlled, establishing a causal relationship is not difficult.

Six key issues that are addressed in the data evaluation of human and animal studies are the following:

1. *Evidence of adverse effects in humans.* In the hazard identification step, all human, animal, and *in vitro* published evidence addressing the likelihood of a nutrient eliciting an adverse effect in humans is examined. Decisions regarding which observed effects are "adverse" are based on scientific judgments. Although toxicologists generally regard any demonstrable structural or functional alteration to represent an adverse effect, some alterations may be considered of little or self-limiting biological importance.

2. *Causality.* Is a causal relationship established by the published human data? Criteria for judging the causal significance of an exposure-effect association indicated by epidemiologic studies have been adopted by two reports, *Diet, Nutrition, and Cancer* (NRC, 1982) and *Diet and Health* (NRC, 1989b). These criteria include: demonstration of a temporal relationship, consistency, narrow confidence intervals for risk estimates, a biological gradient, specificity, biological plausibility, and coherence.

3. *Relevance of experimental data.* Consideration of the following issues can be useful in assessing the relevance of experimental data.

- *Animal data.* Animal data may be of limited utility in judging the toxicity of nutrients, because of highly variable interspecies differences in nutrient requirements. Nevertheless, all such data should be considered in the hazard identification step, and explicit reasons should be given whenever such data are judged not relevant to human risk.
- *Route of exposure.*[1] Data derived from studies involving ingestion exposure (rather than inhalation or dermal exposure) are most useful for the evaluation of nutrients. Data derived from studies involving inhalation or dermal routes of exposure may be considered relevant if the adverse effects are systemic and data are available to permit interroute extrapolation.
- *Duration of exposure.* Because the magnitude, duration, and fre-

[1]The terms *route of exposure* and *route of intake* refer to how a substance enters the body, for example, by ingestion, inhalation, or dermal absorption. These terms should not be confused with *form of intake,* which refers to the medium or vehicle used—for example, supplements, food, or drinking water.

quency of exposure can vary considerably in different situations, consideration needs to be given to the relevance of the exposure scenario (for example, chronic daily dietary exposure versus short-term bolus doses) to dietary intakes by human populations.

4. *Mechanisms of toxic action.* One active area of research in toxicology is the study of the molecular and cellular events underlying the production of toxicity. Knowledge of such mechanisms can assist in dealing with the problems of interspecies and high-to-low dose extrapolation. In the case of nutrients, it may also aid in understanding whether the mechanisms associated with toxicity are those associated with deficiency. In most cases, however, because knowledge of the biochemical sequence of events resulting from toxicity and deficiency is still incomplete, it is not yet possible to state with certainty whether or not these sequences share a common pathway. Iron, the most thoroughly studied trace element, may represent the only exception to this statement. Deficient to near-toxic exposures share the same pathway, which maintains controlled oxygen transport and catalysis. Toxicity sets in when the exposure exceeds the specific iron-complexing capacity of the organism, resulting in free iron species initiating peroxidation.

5. *Quality and completeness of the database.* The scientific quality and quantity of the database are evaluated. Human or animal data are reviewed for suggestions that the substances have the potential to produce additional adverse health effects. If suggestions are found, additional studies may be recommended.

6. *Identification of distinct and highly sensitive subpopulations.* Some highly sensitive subpopulations have responses (in terms of incidence, severity, or both) to the agent of interest that are clearly distinct from the responses expected for the healthy population. The risk assessment process recognizes that there may be individuals within any life stage group that are more biologically sensitive than others. The ULs derived for nutrients in this document are based on protecting the most sensitive members of a healthy population. For some substances, however, there may be distinct subgroups who have extreme sensitivities that do not fall within the range of sensitivities expected for the healthy population. Whenever data suggest the existence of such subgroups, the UL for the healthy population may not be protective for them. As indicated earlier, the extent to which a sensitive subpopulation will be included in the derivation of a UL for the healthy population is an area of judgment to be addressed on a case-by-case basis.

Dose-Response Assessment

The process for deriving the UL is described in this section and is summarized in Box 3-1. It includes selection of the critical data set, identification of a critical endpoint with its NOAEL (or LOAEL), and assessment of uncertainty.

Box 3-1
Development of Tolerable Upper Intake Levels (ULs)

HAZARD IDENTIFICATION

Components

- Evidence of adverse effects in humans
- Causality
- Relevance of experimental data
- Mechanisms of toxic action
- Quality and completeness of the database
- Identification of distinct and highly sensitive subpopulations

DOSE-RESPONSE ASSESSMENT

Components

- Data selection
- Identification of no-observed-adverse-effect level (NOAEL) (or lowest-observed-adverse-effect level [LOAEL]) and critical endpoint
- Uncertainty assessment
- Derivation of a UL
- Characterization of the estimate and special considerations

Data Selection

The data evaluation process results in the selection of the most appropriate or critical data set(s) for deriving the UL. Selecting the critical data set includes the following considerations:

- Human data are preferable to animal data.
- In the absence of appropriate human data, information from an animal species whose biological responses are most like those of humans is most valuable.
- If it is not possible to identify such a species or to select such

data, data from the most sensitive animal species, strain, or gender combination are given the greatest emphasis.

- The route of exposure that most resembles the route of expected human intake is preferable. This includes considering the digestive state, (for example, fed or fasted), of the subjects or experimental animals. Where this is not possible, the differences in route of exposure are noted as a source of uncertainty.
- The critical data set defines a dose-response relationship between intake and the extent of the toxic response known to be most relevant to humans. One additional issue examined during the evaluation of dose-response data concerns the bioavailability of the nutrient under review. For example, it is known that different metal salts can display different degrees of bioavailability. If the database involves studies of several different salts (for example, iron or chromium valence states), and the effect of the nutrient is systemic, then apparent differences in the degree and/or form of the toxic response among different salts may simply reflect differences in bioavailability. Data on bioavailability are considered and adjustments in expressions of dose-response are made to determine whether any apparent differences in response can be explained.
- The critical data set should document the route of exposure and the magnitude and duration of the intake. Furthermore, the critical data set should document the intake that does not produce adverse effects, the NOAEL, as well as the intake producing toxicity.

Identification of NOAEL (or LOAEL) and Critical Endpoint

The NOAEL can be identified from evaluation of the critical data set. If there are not adequate data demonstrating a NOAEL, then a LOAEL may be used. A nutrient can produce more than one toxic effect (or endpoint), even within the same species or in studies using the same or different exposure durations. The NOAELs (and LOAELs) for these effects will differ. The critical endpoint used in this report is the adverse biological effect exhibiting the lowest NOAEL (for example, the most sensitive indicator of a nutrient's toxicity). The derivation of a UL based on the most sensitive endpoint will ensure protection against all other adverse effects.

Uncertainty Assessment

As discussed previously and further elaborated in Appendix C, several judgments must be made regarding the uncertainties and thus uncertainty factor (UF) associated with extrapolating from the

observed data to the healthy population. Applying UFs to a NOAEL (or LOAEL) will result in a value for the derived UL that is less than the experimentally derived NOAEL, unless the UF is 1.0. The larger the uncertainty, the larger the UF and the smaller the UL, which represents a lower estimate of the threshold above which the risk of adverse effects may increase. This is consistent with the ultimate goal of the risk assessment: to provide an estimate of a level of intake that will protect the health of the healthy population (Mertz et al., 1994).

Although several reports describe the underlying basis for UFs (Dourson and Stara, 1983; Zielhuis and van der Kreek, 1979), the strength of the evidence supporting the use of a specific UF will vary. Because the imprecision of these UFs is a major limitation of risk assessment approaches, considerable leeway must be allowed for the application of scientific judgment in making the final determination. While the UFs selected for nonessential chemical agents are usually multiples of 10, the data on nutrient toxicity may not be subject to the same uncertainties as with nonessential chemical agents since data are generally available regarding intakes of human populations. The UFs for nutrients are typically less than 10 depending on the quality and nature of the data and the adverse effects involved. Also, smaller UFs may be used when the adverse effects are extremely mild and reversible.

In general, when determining a UF, the following potential sources of uncertainty are considered:

- *Interindividual variation in sensitivity.* Small UFs (in the range of 1 to 10) are used if it is judged that little population variability is expected for the adverse effect, and larger factors (greater than 10) are used if variability is expected to be great (NRC, 1994).
- *Experimental animal to human.* A UF is generally applied to the NOAEL to account for the uncertainty in extrapolating animal data to humans. Smaller or larger UFs (greater than 10) may be used if it is believed that the animal responses will over- or underpredict average human responses (NRC, 1994).
- *LOAEL to NOAEL.* If a NOAEL is not available, a UF may be applied to account for the uncertainty in deriving a UL from the LOAEL. The size of the UF involves scientific judgment based on the severity and incidence of the observed effect at the LOAEL and the steepness (slope) of the dose response.
- *Subchronic NOAEL to predict chronic NOAEL.* Scientific judgment is necessary to determine whether chronic exposure is likely to lead to adverse effects at lower intakes than those produc-

ing effects after subchronic exposures, when data are lacking on chronic exposures.

Selection of a UF for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride

The selection of a UF of approximately 1.0 for fluoride and magnesium is primarily based on the very mild (and in the case of magnesium, reversible) nature of the adverse effects observed. A slightly larger UF (1.2) was selected for vitamin D intake in adults and other life stage groups except infants as the short duration of the study used (Narang et al., 1984) and the small sample size supports the selection of a slightly larger UF. For vitamin D in infants, a larger UF (1.8) was selected due to the insensitivity of the critical endpoint, the small sample sizes of the studies, and limited data about the sensitivity at the tails of the distribution. A UF of 2 was selected for calcium to account for the potential increased susceptibility to high calcium intake by individuals who form renal stones and the potential to increase the risk of mineral depletion in vulnerable populations due to calcium-mineral interactions. A UF of 2.5 was selected for phosphorus due to the lack of information on potential adverse effects in the range between normal phosphorus levels and levels associated with ectopic mineralization. The selection of a UF for phosphorus that is larger than those for the other nutrients evaluated is also due to the relative lack of human data describing adverse effects of excess phosphorus intake.

Derivation of a UL

The UL is derived by dividing the NOAEL (or LOAEL) by all the relevant UFs. The derivation of a UL involves the use of scientific judgment to select the appropriate NOAEL (or LOAEL) and UF. The framework or model outlined in this chapter for characterizing the potential risk (for example, scientific judgment used in deriving a UL from a NOAEL [or LOAEL]) is provided from a nutritional risk assessment perspective. This perspective is consistent with that of classical risk assessment in that it requires explicit consideration and discussion of all choices made, both regarding the data used and the uncertainties accounted for.

Characterization of the Estimate and Special Considerations

ULs are derived for various life stage groups utilizing relevant

databases, NOAELs and LOAELs, and UFs. In cases where no data exist with regard to NOAELs or LOAELs for the group under consideration, extrapolations from data in other age groups and/or animal data are made on the basis of known differences in body size, physiology, metabolism, absorption, and excretion of the nutrient.

If the data review reveals the existence of subpopulations having distinct and exceptional sensitivities to a nutrient's toxicity, these subpopulations are considered under the heading "Special Considerations."

GLOSSARY

Bioavailability: The accessibility of a nutrient to participate in metabolic and/or physiological processes.

Dose-Response Assessment: The second step in a risk assessment in which the relationship between nutrient intake and adverse effect (in terms of incidence and/or severity of the effect) is determined.

Hazard Identification: The first step in a risk assessment, which is concerned with the collection, organization, and evaluation of all information pertaining to the toxic properties of a nutrient.

Lowest-Observed-Adverse-Effect Level (LOAEL): The lowest intake (or experimental dose) of a nutrient at which an adverse effect has been identified.

No-Observed-Adverse-Effect Level (NOAEL): The highest intake (or experimental dose) of a nutrient at which no adverse effects have been observed.

Risk: Within the context of nutrient toxicity, the probability or likelihood that some adverse effect will result from a specified excess intake of a nutrient.

Risk Assessment: An organized framework for evaluating scientific information, which has as its objective a characterization of the nature and likelihood of harm resulting from excess human exposure to an environmental agent (in this case, a dietary nutrient). It includes the development of both qualitative and quantitative expressions of risk. The process of risk assessment can be divided into four major steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization.

Risk Characterization: The final step in a risk assessment, which summarizes the conclusions from Steps 1 through 3 of the risk assessment and evaluates the risk. This step also includes a char-

acterization of the degree of scientific confidence that can be placed in the UL.

Risk Management: The process by which risk assessment results are integrated with other information to make decisions about the need for, method of, and extent of risk reduction. In addition to risk assessment results, risk management considers such issues as the public health significance of the risk, the technical feasibility of achieving various degrees of risk control, and the economic and social costs of this control.

Tolerable Upper Intake Level (UL): The maximum level of total chronic daily intake of a nutrient or food component that is unlikely to pose risks of adverse effects to the most sensitive members of the healthy population.

Uncertainty Factor (UF): A number by which the NOAEL (or LOAEL) is divided to obtain the UL. UFs are used in risk assessments to deal with gaps in data (for example, data uncertainties) and knowledge (for example, model uncertainties). The size of the UF varies depending on the confidence in the data and the nature of the adverse effect.